REMARKS/ARGUMENTS

Claims 1-46 are pending in this application and presented for examination. Claims 1 and 29 (withdrawn) have been amended to more particularly point out and distinctly claim the subject matter. Claims 1-3, 18, 19, 22, 23 and 26 were examined in the previous Office Action. No new matter has been introduced with the foregoing claim amendments. Reconsideration is respectfully requested in view of the remarks below.

I. FORMALITIES

Claims 1 and 29 have been amended to more particularly point out and distinctly claim the subject matter of the invention. Support for the amendment is found, for example, on page 8, line 14 wherein it states that the at least one anchor "entraps the target nucleic acid." Further support is found, for example, in Figures 1 B, C and D, wherein various embodiments of "entrapment" of the target nucleic acid are shown. As such, no new matter has been introduced, and Applicant requests that the Examiner enter the amendments.

Applicant acknowledges with appreciation that the Examiner has withdrawn the anticipation rejection of Yao *et al.,* in view of the earlier response. The Examiner has, however, reintroduced an enablement rejection, which had been previously overcome.

II. REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1-3, 18-19 and 26 under 35 U.S.C. § 102(b) as allegedly being anticipated by Motz *et al.*, *JBC* vol. 277, No. 18, 16179-16188, 2002 ("Motz *et al.*"). The Examiner states that there is no requirement in the claims that the attachment complex be covalently bound to the polymerase. The Examiner also alleges that there are no structural requirements in the claims regarding the anchor and the attachment complex. To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

In the rejection, the Examiner states that Motz *et al.* teach a PCNA binding domain as allegedly "an anchor" and the PCNA allegedly as "an attachment complex." In Motz *et al.*, the PCNA binding domain and the PCNA are clearly two different and distinct components. In addition, the "attachment complex" of Motz *et al.* encircles the DNA.

Applicants have amended claim 1 as follows:

> 1. (Currently amended) A polymerase-nucleic acid complex for increasing the processivity index, said polymerase-nucleic acid complex comprising:
>
> a target nucleic acid and a nucleic acid polymerase, wherein said polymerase has at least one anchor having one end covalently attached thereto, wherein the other end of the anchor is i) attached to said polymerase, ii) to a topological tether or iii) to a support, which serves to entrap said target nucleic acid; and
>
> an attachment complex comprising said at least one anchor, wherein during replication, said attachment complex irreversibly associates said target nucleic acid with said polymerase until replication is complete, thereby increasing the processivity index.

As amended, claim 1 is in no way anticipated by Motz *et al.* For example, the anchor in the subject application is *part* of the attachment complex, whereas in Motz *et al.* there exists two distinct components. In addition, as presently claimed, it is the anchor as part of the attachment complex which entraps the DNA and irreversibly associates the polymerase and the nucleic acid. In Motz *et al.*, the second component holds the DNA and cycles off. Further, in the instant claims, although one end of the anchor is attached to the polymerase, the other end of the anchor is attached to 1) the polymerase, ii) a tether or iii) a support. The present anchor has two ends, both of which are attached ("anchored"). In Motz *et al.*, the first component is grafted to the carboxy terminus and presumably becomes the new carboxy terminus. The claimed features are simply not taught by Motz *et al.* As such, Applicant requests that the Examiner withdraw the rejection.

III. FIRST REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 19 and 22 under 35 U.S.C. § 103(a) as allegedly being obvious over Motz *et al.* and U.S. Patent No. 5,198,543 ("Blanco *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

In the present claims, the anchor entraps the DNA, not the second component or PCNA (the "attachment complex" as the Examiner has referred to it). Further, although one end of the anchor is attached to the polymerase, the other end of the anchor is attached to 1) the polymerase, ii) a tether or iii) a support. Each of these features distinguish over Motz *et al.* Blanco *et al.* do not supply the deficiencies of the primary reference. Blanco *et al.* do not teach or even suggest an attachment complex, nor a covalently attached anchor. Blanco *et al.* teach a modified ϕ29 polymerase with a modified exonuclease activity. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

IV. SECOND REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claim 23 as allegedly being obvious over U.S. Patent No. 6,255,083 ("Williams") and Motz *et al.* To the extent that the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

Williams do not teach or suggest an anchor that entraps the DNA as currently taught and claimed. In the present invention, one end of the anchor is attached to the polymerase, whereas the other end of the anchor is attached to 1) the polymerase, ii) a tether or iii) a support.

Motz *et al.* do not supply the deficiencies of the primary reference. Each of the claimed features of the anchor and attachment complex distinguishes over Motz *et al.* Motz *et al.* in no way teach the foregoing features, nor suggest their modification. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

V. REJECTION UNDER 35 U.S.C. § 112, Written Description

Claims 1-3, 18, 19, 22, 23 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the written description requirement. The Examiner alleges that the claims read on any polymerase and there is insufficient written description in the specification to support broad claims. In response, Applicant respectfully traverses the rejection.

As the Examiner can appreciate, although the polymerase is a key component to the invention, "the type of polymerase" or "specific polymerase" is not critical. The Examiner's rejection is more akin to a rejection when claiming *new* polymerases such as in a new genus claim. However, Applicant is not claiming *new* polymerases per se, but modifying polymerases to make them new.

Applicant has listed in the specification a number of polymerases suitable for use in the present invention. In this regard, the Examiner's attention is respectfully directed to paragraphs 57-60, wherein it states:

> [0057] The polymerases suitable for use in the present invention preferably have a fidelity (incorporation accuracy) of at least 99%. In addition, the processivity of the polymerase should be at least 20 nucleotides, prior to immobilization. Although the polymerase selected for use in this invention is not critical, preferred polymerases are able to tolerate labels on the γ-phosphate of the NTP.
>
> [0058] In certain aspects, the polymerases useful in the present invention are selected from the A family polymerases or the B family polymerases. DNA-dependent DNA polymerases have been grouped into families, including A, B, X, and others on the basis of sequence similarities. Members of family A, which includes bacterial and bacteriophage polymerases, share significant similarity to E. coli polymerase I; hence family A is also known as the pol I family. The bacterial polymerases also contain an exonuclease activity, which is coded for in the N-terminal portion. Family A polymerases include for example, Klenow, Taq, and T7 polymerases. Family B polymerases include for example, the Therminator polymerase, phi29, RB-69 and T4 polymerases.

> [0059] In certain instances, suitable DNA polymerases can be modified for use in the present invention. These polymerases include, but are not limited to, DNA polymerases from organisms such as Thermus flavus, Pyrococcus furiosus, Thermotoga neapolitana, Thermococcus litoralis, Sulfolobus solfataricus, Thermatoga maritima, E. coli phage T5, and E. coli phage T4. The DNA polymerases may be thermostable or not thermostable.
>
> [0060] In other embodiments, the polymerases include T7 DNA polymerase, T5 DNA polymerase, HIV reverse transcriptase, E. coli DNA pol I, T4 DNA polymerase, T7 RNA polymerase, Taq DNA polymerase and E. coli RNA polymerase. In certain instances, exonuclease-defective versions of these polymerases are preferred. The efficiency with which γ-labeled NTPs are incorporated may vary between polymerases; HIV-1 RT and E. coli RNA polymerase reportedly readily incorporate .gamma.-labeled nucleotide. The polymerase can also be a T7 polymerase. T7 polymerase has a known 3D structure and is known to be processive. In order to operate in a strand-displacement mode, the polymerase requires a complex of three proteins: T7 polymerase+thioredoxin+primase (Chowdhury et al. PNAS 97:12469). In other embodiments, the polymerases can also be HIV RT and DNA Polymerase I.

The Examiner cites three CAFC cases in support of the alleged lack of written description. The *Regents of the University of California v Eli Lily* case involved generically recited cDNA encoding vertebrate insulin as a new composition of matter. Not a *known cDNA* which was later modified. Similarly, in *Fiers v Sugano*, which was actually decided before *Eli Lily*, the Court considered a product, a DNA sequence coding for a protein that promoted viral resistance in human tissue. The Federal Circuit rejected an argument that the existence of a workable method for preparing a DNA sequence establishes its conception. 25 U.S.P.Q.2d at 1604. The Court explained that its "statement in Amgen that conception may occur, inter alia, when one is able to define a chemical by its method of preparation requires that the DNA be claimed by its method of preparation." 25 U.S.P.Q.2d at 1604 05. The Court noted that chemical materials may be claimed by structure or physical properties, or also through a product by process claim. Finally, *Vas-Cath Inc. v Mahukar* involved the issue as to whether the

specification in a earlier case supports a later filed case. None of these cited cases appear to be on point.

The invention as currently claimed is much different. Applicant is claiming *a polymerase* modified to include "accessories" to have longer read lengths. It does not matter which polymerase is modified, only that its processivity is increased. In the specification at paragraph 57, Applicant states "[a]lthough the polymerase selected for use in this invention is not critical, preferred polymerases are able to tolerate labels on the γ-phosphate of the NTP." The representative number of species requirement is an issue when there is substantial variation in the genus. This is not an issue when the type of polymerase is not critical. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

VI. REJECTION UNDER 35 U.S.C. § 112, Enablement

Claims 1-3, 18, 19, 22, 23 and 26 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

The *Wands* Analysis

As the Examiner is aware, a *Wands* analysis sets forth various factors to be considered and weighed. These factors include: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

(i) Level of skill in the art.

The Examiner states that the "the level of skill in the art is deemed to be high." Applicant is in agreement with the Examiner in that work in the field of nucleic acid sequencing

and protein engineering is typically conducted at academic and commercial enterprises having scientists with advanced academic degrees and postdoctoral training in their relevant fields. Accordingly, Applicant submits that the level of skill of those in the art is very high.

***(ii)* Nature of the Invention.**

The subject matter at issue lies in the field of nucleic acid sequencing and protein engineering. This field of art is traditionally one in which a large volume of screening, experimental design and testing is both typical and routine. Further, the claims herein embody a creative pioneering invention.

***(iii)* Breadth of the claims.**

The Examiner characterizes the invention as follows:

> Claims 1-3, 18, 19, 22, 23 and 26 are broadly drawn to a polymerase-nucleic acid complex, in which the polymerase comprises an attachment complex which comprises at least one anchor covalently attached to the polymerase. However, as will be further discussed, **there is no support in the specification and prior art for the structure as claimed**. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316,1330 (Fed. Cir. 2001). [Emphasis added]

Applicant has amended the claims to more particularly point out and distinctly claim the subject matter of the invention. Applicant agrees with the Examiner with respect to the comment that there is "no support in the prior art," for the claimed invention, *i.e.*, the invention is novel and unobvious. Applicant respectfully points out that the art rejections above appear contrary in view of this comment. In any event, the specification is replete with teaching and disclosure of the claimed invention.

With respect to the claim scope, the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the

claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Here, the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. With the clear guidance provided by the detailed Specification, 11 Examples and 12 Drawings, one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

(iv) Amount of Guidance Presented and (v) working examples

The Examiner alleges:

Working Examples

> The specification has no working examples of any polymerases comprising an attachment complex which irreversibly associates the polymerase with a target nucleic acid.

In this regard, the Examiner's attention is respectfully directed to the enclosed Information Disclosure Statement, JGK Williams *et al.*, *Nucleic Acid Research* 2008, Vol. 36, No. 18, pp 1-11. On page 2 of the reference, the authors state the following:

> In this report, we describe an artificial processivity complex that *both traps the template DNA on the polymerase and facilitates oriented immobilization on biotinylated surfaces*. Starting with the parent polymerase (above) adapted to phosphate-labeled dNTPs, we inserted AviTag™ peptide 'legs' at two surface-exposed locations flanking the DNA-binding cleft. The AviTag peptides provide highly specific sites for enzymatic biotinylation of the polymerase by E. coli biotin–protein ligase. Processivity is

> enhanced with streptavidin binding the AviTag legs, retaining the template in the DNA-binding cleft. We show that the template DNA is stably associated with the polymerase, and that the polymerase–DNA–streptavidin complexes are active both in solution and when immobilized on biotinylated coverglass surfaces. *We demonstrate that the clamp converts a naturally nonprocessive DNA polymerase into a highly processive one capable of incorporating thousands of nucleotides without dissociating from the template.* [Emphasis added].

The foregoing reference unequivocally demonstrates that the claimed invention works. The anchor and attachment complex as claimed *convert a naturally nonprocessive DNA polymerase into a highly processive one capable of incorporating thousands of nucleotides without dissociating from the template.* This reference demonstrates that the claimed invention is fully enabled.

Moreover, the specification shows no fewer than 11 Examples on how to make and use the claimed invention. Under MPEP § 2164.01(b) as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied.

The Examiner alleges:

> Guidance in the Specification.
>
> The specification provides no evidence that the claimed polymerase can be produced as claimed. *The only mention of any specific polymerase is in paragraph [0050] and [0051] on pages 11 and 12, where it mentions a Therminator polymerase (no specific amino acid sequence provided)which has two peptides attached to amino acid positions K53 and K229. No such polymerase was produced by Applicant and there is no evidence that it would function as claimed.* Considering the large number of polymerases with differing structures and function, i.e., DNA- and RNA-dependent DNA polymerases and RNA- and DNA-dependent RNA polymerases, for example, the guidance

> provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. [Emphasis added].

In this regard, the Examiner's attention is respectfully drawn to page 2 of the aforementioned reference, under the heading of "Polymerase AviTag constructs." As described therein:

> The starting enzyme was a mutant of Therminator DNA polymerase (http://www.neb.com) adapted by directed evolution for efficient utilization of phosphate-labeled nucleotides (manuscript in preparation). AviTag is a peptide substrate for E. coli biotin–protein ligase which, when fused to a target protein, provides a site for efficient enzymatic biotinylation (http://www.avidity.com). The overlapping primer PCR method of Chiu et al. (27) *was used to insert AviTag in the mutant polymerase at two positions (Therminator coordinates K53-V54 and K229-F230). The 21-amino acid insertion ssGLNDIFEAQ KIEWHEgass comprises AviTag (upper case) flanked by arbitrarily chosen amino acids (lower case)*; enzymatic biotinylation occurs at the epsilon-amine of the lysine (K). The starting plasmid was a 6.4-kb pBAD-HisC plasmid (Invitrogen) containing the mutant polymerase gene. [Emphasis added].

The reference acknowledges that the claimed invention works as described. Moreover, there should not be any concern regarding the type or number of polymerases, as many polymerases can be modified to be used in the present invention. As is apparent from the foregoing, the amount of guidance and the number of working examples in the specification at the very least satisifies and more likely far exceeds the enablement requirements of 35 U.S.C. § 112, first paragraph.

(vi) State of the Art (vii) Predictability in the Art

The Examiner alleges:

The unpredictability of the art and the state of the prior art

> There is a great deal of unpredictability in the modification of structural properties of polymerases, due to the diversity of their amino acid sequences and corresponding three-dimensional structures. As evidenced by Braithwaite et al. (Nucl. Acids Res., vol. 21, pp. 787-802, 1993), in 1993 there were three families of DNA polymerases (A, B and C) and about 56 known amino acid sequences (page 787, Fig. 1). As can be seen from Table 1 (page 800), the polymerases have different amino acid sequences and properties. Brautigam et al. (Curr. Opinion Struct. Biology, vol. 8, pp. 54- 63, 1998) presented a review of known structures of DNA and RNA polymerases. Even though the polymerases in general share certain similarities of the polymerase domain, the details of the structures differ from polymerase to polymerase even within a single family (Fig. 2; page 58, fifth paragraph; page 62, last paragraph). Therefore, since the structure of any given protein is influenced by all of its components, introduction of mutations or additional structural elements is by no means routine in terms of obtaining a functional protein.

In response to these allegations, Applicant respectfully points out that the PNAS reference (Patel *et al. PNAS*, Vol. 97, 5095-5100, 2000) in the Information Disclosure Statement states at page 1, column 1, second paragraph under the Abstract:

> *All DNA and RNA polymerases share two conserved regions: motif A and motif C.* Both are located within the palm subdomain. Structural data show that amino acids within motif A are in position to interact with the incoming dNTP, coordinate with the two divalent metal cofactors, and interact with the fingers subdomain during the conformation change step after dNTP binding (3, 4).

Further, the Patel reference states in the same paragraph:

> ***The primary amino acid sequences of various DNA polymerase active sites are exceptionally conserved***, suggesting that motif A evolved slowly. Motif A retains the sequence DYSQIELR in polymerases from organisms separated by many million years of

> evolution, including Thermus aquaticus, Chlamydia trachomatis, and Escherichia coli. Structurally, motif A is superimposable with a mean deviation of 1 Å among mammalian pol a and prokaryotic pol I family DNA polymerases (7) and begins at an antiparallel b-strand containing predominantly hydrophobic residues and continues to an a-h (Fig. 1). *Taken together, these results indicate that polymerases function by similar catalytic mechanisms and that the active site of polymerases may be immutable to ensure the survival of organisms.* [Emphasis added].

Thus, according to Patel, the region that the instant invention is most concerned with *i.e.*, the polymerases' active site, is conserved in *all* polymerases, whether its DNA or RNA polymerases, mammalian or prokaryotic. Motif A is superimposible with a mean deviation of only 1 Å. In view of this reference, the Examiner's concerns regarding the number and kind of polymerases as claimed vis a vis enablement is completely alleviated.

The Examiner further alleges:

> This is supported by evidence provided by Barnes (U.S. Patent No. 5,436,149 A), which discloses construction of a thermostable DNA polymerase which can remain functional above 97° C. The constructs involved deletions of amino acids 1-278, 1-288 and 1-291 of Thermus aquaticus DNA polymerase (col. 5, lines 60-68; col. 6, lines 1-55), and the best result was obtained with a polymerase which had residues 1-278 removed (Fig. 4, for example). Therefore, deletion of only additional 10 or 13 amino acids markedly changed the thermostability properties of the enzyme. As stated by Barnes (col. 1, lines 67 and 68; col. 2, lines 1-17):
>
> "The development of other enzymatically active mutein derivatives of Thermus aquaticus DNA polymerase is hampered, however, by the unpredictability of the impact of any particular modification on the structural and functional characteristics of the protein. Many factors, including potential disruption of critical bonding and folding patterns, must be considered in modifying an enzyme and the DNA for its expression. A significant problem associated with the creation of N-terminal deletion muteins of high-temperature Thermus aquaticus DNA polymerase is the prospect that the amino terminus

> of the new protein may become wildly disordered in the higher temperature ranges, causing unfavorable interactions with the catalytic domain(s) of the protein, and resulting in denaturation."
>
> In conclusion, any modification of a protein structure requires extensive testing to verify that the desired properties are obtained and that the protein retains its function.

U.S. Patent No. 5,436,149 to Barnes is drawn to recombinant DNA sequence encoding a DNA polymerase having an amino acid sequence comprising substantially the same amino acid sequence as the Thermus aquaticus or Thermus fiavus DNA polymerase, excluding however the N-terminal *280 amino acid residues* of WT Thermus aquaticus or the N-terminal *279 amino acids* of Thermus flavus DNA polymerase. (see, column 3, lines 43-53). Applicant is not engineering thermostability into polymerases. Applicant is engineering at least one anchor which entraps the nucleic acid to enhance processivity. Thus, even if Barnes teach that a 10 or 13 amino acid change makes a difference in thermostability as the Examiner alleges, it does not make a difference with respect to the claimed invention. The claimed invention is drawn to longer read lengths. So, if the polymerases of Barnes were engineered such that the polymerase has at least one anchor having one end covalently attached thereto, wherein the other end of the anchor is i) attached to said polymerase, ii) to a topological tether or iii) to a support, which serves to entrap the target nucleic acid; and an attachment complex comprising the at least one anchor, wherein during replication, the attachment complex irreversibly associates said target nucleic acid with the polymerase, processivity would be sure to increase.

> Quantity of Experimentation
> The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to produce claimed polymerases, including selection of possible anchoring sites for each of the polymerases, different types of anchors (peptides, nucleic acids, etc), influence of the modification on the protein structure and processivity, influence of reaction conditions (pH, temperature, type of nucleotides used). This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any

guarantee of success in the succeeding steps.

Applicant acknowledges that no art is without its uncertainty. However, the invention works as claimed. Moreover, there is clear guidance provided by the detailed Specification, 11 Examples and 12 Drawings filed with the application which are ample teaching and instruction with respect to the invention now claimed. 35 U.S.C. § 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In this case, both the Applicant and the Examiner are in agreement with respect to "the level of skill in the art is deemed to be high."

The Examiner states that there is uncertainty with respect to polymerase structure and therefore, uncertainty exists with respect to the influence of the mutation on the polymerase functionality.

As a class of enzymes, more mutations are performed on polymerases than probably any other enzyme class. Scores of scholarly articles, journal references and texts have been written on the subject. In fact, a great deal of practical guidance is in the art on the methodologies to achieve mutation and retain activity. Given the flexibility in achieving a functional polymerase with an attachment complex, Applicant submits that many mutations can be made in any polymerase, wherein anchors are engineered and if necessary, used to immobilize the enzyme.

In addition, despite the Examiner's misgivings about the modified polymerase functioning as a polymerase, the Williams reference clearly demonstrates that the invention works as claimed. Thus, the engineered polymerase-DNA complexes of the present invention are active and improve processivity.

(vii) Undue Experimentation.

As set forth in the MPEP §2164.06, "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the

specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

However, time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989). Time and difficulty of experiments are not determinative if they are merely routine. Given the expert and explicit guidance of the Specification, 11 Examples and 12 Drawings, coupled with the high level of skill in the art, any experiments would be merely routine.

(viii) Summary and Overall *Forman/Wands* Analysis.

As set forth in the MPEP §2164.01(a), the final step in making the determination that "undue experimentation" would have been needed to make and use the claimed invention is reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 737."

Here, both the Applicant and the Examiner are in agreement that the level of skill for one of ordinary skill in the art is very high. Given the expert and explicit guidance of the Specification, 11 Examples and 12 Drawings, coupled with the high level of skill in the art, any experiments would be merely routine. In light of the above remarks, Applicant believes that one of ordinary skill in the art can practice the invention as presently claimed according to the requirements of 35 U.S.C. §112, first paragraph. Accordingly, Applicant respectfully requests that the above rejection be reconsidered and withdrawn.

VII. REJECTION UNDER 35 U.S.C. § 112, Clarity

Claims 1-3, 18, 19, 22, 23 and 26 are further rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in that claim 1 recites "wherein said polymerase has an attachment complex comprising at least one anchor covalently attached thereto." The Examiner alleges that it is unclear as to whether the anchor is attached to the polymerase or the

attachment complex. To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

Claim 1 has been amended to clearly recite:

> 1. A polymerase-nucleic acid complex for increasing the processivity index, said polymerase-nucleic acid complex comprising:
>
> a target nucleic acid and a nucleic acid polymerase, wherein said polymerase has at least one anchor having one end covalently attached thereto, wherein the other end of the anchor is i) attached to said polymerase, ii) to a topological tether or iii) to a support, which serves to entrap said target nucleic acid; and
>
> an attachment complex comprising said at least one anchor, wherein during replication, said attachment complex irreversibly associates said target nucleic acid with said polymerase until replication is complete, thereby increasing the processivity index.

In view of the amendment, it is clear that the polymerase has at least one anchor having one end covalently attached to the polymerase, wherein the other end of the anchor is i) attached to the polymerase, ii) to a topological tether or iii) to a support, which serves to entrap the target nucleic acid. Further, the attachment complex comprises the at least one anchor. In view of the amendment to the claims, Applicant respectfully requests that the Examiner withdraw the rejection.

VIII. DOUBLE PATENTING

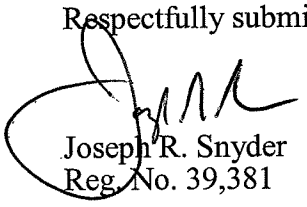
The Examiner has rejected claims 1-3, 23 and 26 on the ground of nonstatutory obviousness-type double patenting as allegedly being obvious over claim 19 of U.S. Patent No. 7,462,468. Without acquiescing to the rejection, Applicants include herewith a Terminal Disclaimer to obviate the double patenting rejection. Accordingly, Applicant requests that the Examiner withdraw the rejection.

IX. CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
JS:js
61904443 v1